(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 October 2003 (02.10.2003)

PCT

(10) International Publication Number
WO 03/080560 A1

(51) International Patent Classification[7]: C07C 213/02, 215/42

(21) International Application Number: PCT/IN02/00131

(22) International Filing Date: 13 June 2002 (13.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
208/mas/2002 26 March 2002 (26.03.2002) IN

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *with amended claims and statement*

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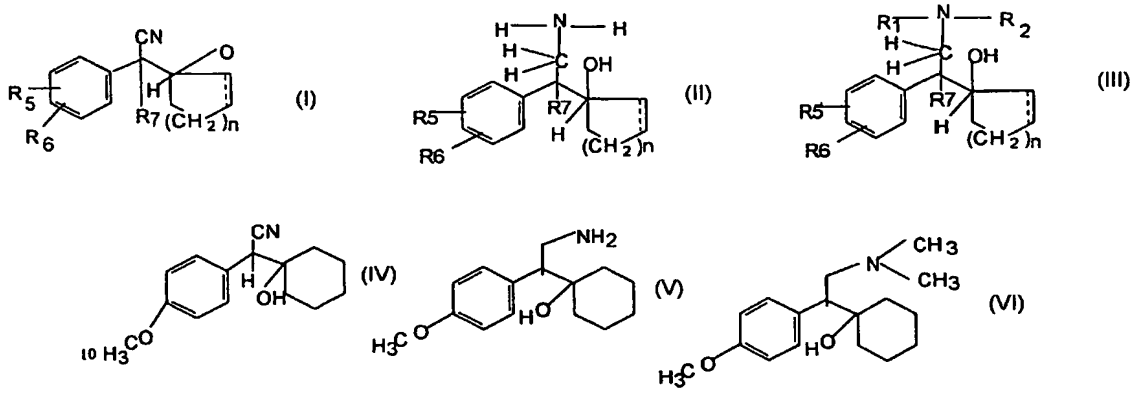
(54) Title: MANUFACTURE OF PHENYL ETHYLAMINE COMPOUNDS, IN PARTICULAR VENLAFAXINE



(57) Abstract: A process for the preparation of hydroxy (cycloalkane/cyclokene) phenylethyl amine of the general formula (III) comprising alkylation of its precursor amine of general formula (II) which is in turn produced by an effective reduction process from its precursor cyanide having the general formula (I) using Raney Nickel (CORMIII) as catalyst where, either of R5 and R6 independently could be in meta or para position and R5, R6 are independently hydrogen, hydroxyl, alkyl, alkoxy, alkanoyloxy, cyano, nitro, alkylmercapto, amino, alkylamino, allkanamido, halo, trifluoromethyl, or taken together methylenedioxy, n is 0,1,2,3,4; R7 is hydrogen or alkyl of 1-7 carbon atom, R1 I H or alkyl of 1-3 carbon atom and R2 is alkyl of 1-3 carbon atom, the dotted line represents optional unsaturation. Compounds of formulae IV, V and VI are respectively derivatives of compounds I, II and III respectively.

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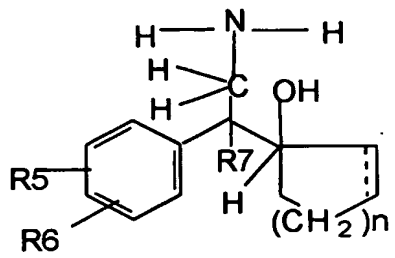
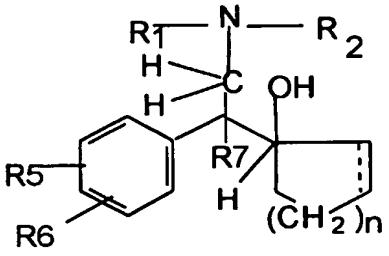
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

MANUFACTURE OF PHENYL ETHYLAMINE COMPOUNDS, IN PARTICULAR VENLAFAXINE.

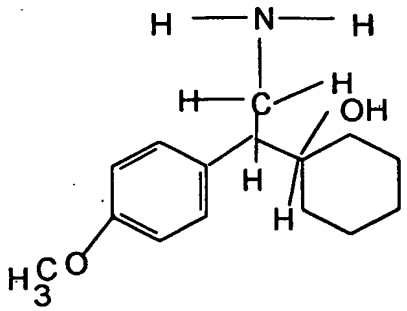
This invention relates to an improved process for the manufacture of hydroxy(cycloalkane or cycloalkene)phenyl ethyl amine compounds of general formula II and its derivatives and in particular the derivative of formula III. More particularly the invention relates to a process for manufacture of precursor of antidepressant of formula V. and its dialkylamino derivative of formula VI.



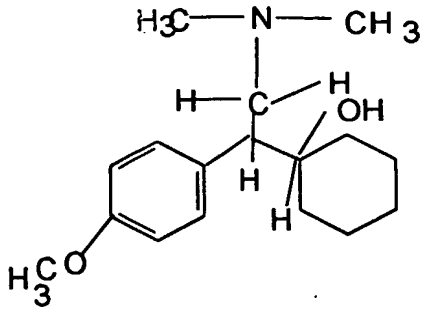
Formula II



Formula III



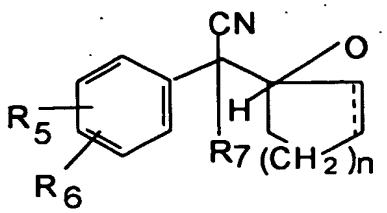
Formula V



Formula VI

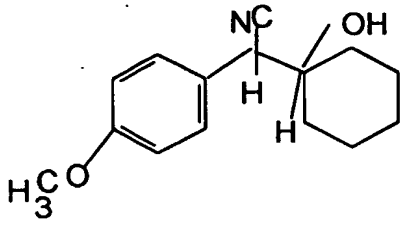
where, either of R5 and R6 independently could be in meta or para position and R5, R6 are independently hydrogen, hydroxyl, alkyl, alkoxy, alkanoyloxy, cyano, nitro, alkylmercapto, amino, alkylamino, alkanamido, halo, trifluoromethyl, or taken together methylenedioxy , n is 0,1,2,3,4; R7 is hydrogen or alkyl of 1-7 carbon atom,.R1 is H or alkyl of 1-3 carbon atom and R2 is alkyl of 1-3 carbon atom ,the dotted line represents optional unsaturation.

The generic version of the antidepressants is represented as formula III and its precursor amine as formula II, and precursor of the amine of formula II is a nitrile of the compound of formula I



Formula I

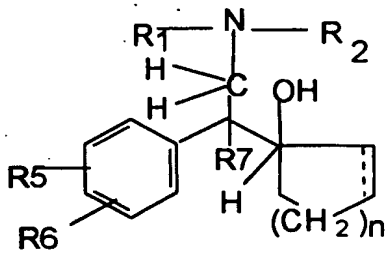
When in formula I either R5 or R6 is in para position and either one of them is -OCH3 and the other is H; R7 is hydrogen; the dotted line representing optional unsaturation is removed ; and n = 2 the compound of formula I is a compound of formula IV which is known as 1-[cyano-(p_methoxyphenyl)methyl]cyclohexanol.



Formula IV

PRIOR ART

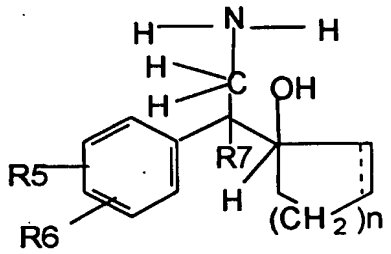
Hydroxy (cyclokene or cycloalkane) (di alkyl) amino phenyl ethyl compound has the generic formula



Formula III

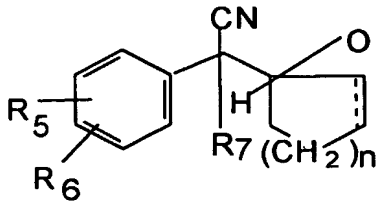
The compound of this general formula has been described in US 4,535,186 and J.Med.Chem33,2809-2905

The said US 4,535,186 and its corresponding EP 0112668A2 teaches the art of manufacture of compound of formula III from its precursor of formula II



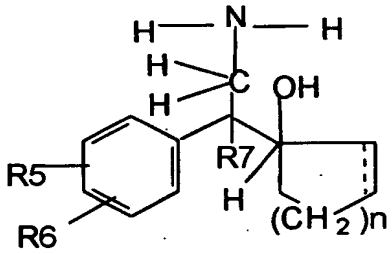
Formula II

The formula II in its turn is arrived at by the reduction of a cyano compound of formula I. The overall process of synthesis of compound of formula III is as under.



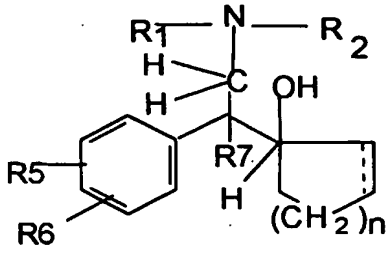
Formula I

Reduction



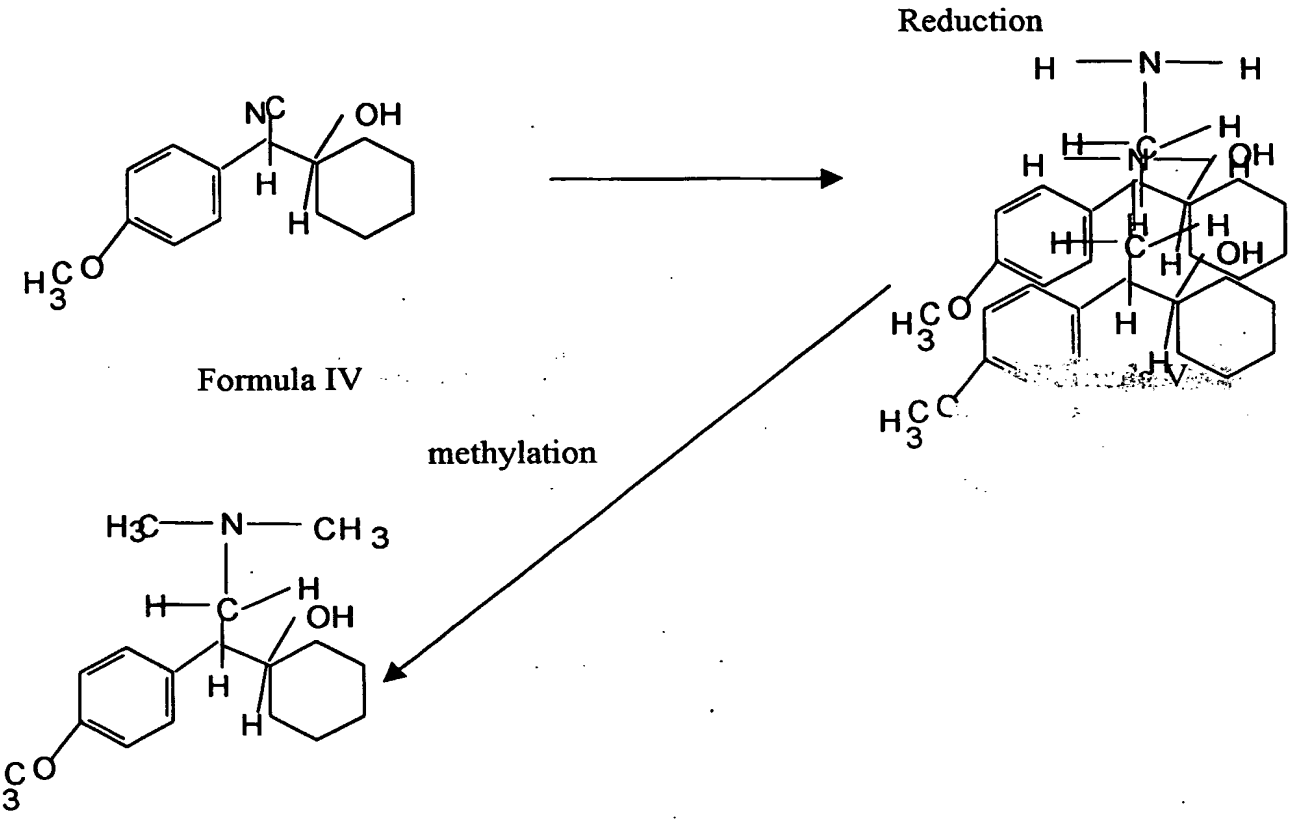
Formula II

Alkylation



Formula III

Reduction of the compound of formula IV gives the compound of formula V, which is chemically known as 1-[2-amino-1-(p-methoxyphenyl)ethyl] cyclohexanol. Methylation of compound of formula V will produce the compound of formula VI which is chemically known as 1-[2-dimethyl (p-methoxyphenyl)ethyl]cyclohexanol or venlafaxine.



Formula IV

Formula VI

The reduction process is depicted as above is carried out as follows :

J.Med.Chem 33,2809-2905 ; US 4,535 ,186 and its corresponding EP 0112668A2 teaches the art of reduction of generic version of venlafaxine as well as venlafaxine as under

Catalyst :Raney NickelCorm III

Solvent:Methanol:Methanol ammonia (2:1)

Temp:room temp.

Pressure: 5 Kg/cm2 (72psi)

Time 9hrs

EP 0112669 teaches the various reduction condition as under

Pd/C (10%) and hydrogen in ethanol media

Lithium aluminium hydride in acid media

Rhodium Alumina in ammoniacal ethanol to reduce the nitrile to primary amine

Yet another disclosure WO/0059851 and WO/32556 the said reduction has been carried out using CoCl2 and NaBH4.

According to Chang et al. The precursor cyano methyl compound of the formula IV can be reduced by Na BH4 and BF3 etherate to compound of formula V.

However the above process has one or other disadvantages as depicted as under.

1. Use of expensive organic catalyst like Rh/Al2O3 and BF3 etherate.
2. Use of costly reducing agent like NaBH4.
3. Most of the cases shown above the reducing agent are prone to fire hazard.

The use of Raney Ni, however, reduces the cost of reduction process as the catalyst can be recycled a number of times and hydrogen is a cheaper reducing agent.

Alkylation is performed after the preparation of the primary amine. Methylation of the primary amine is however a well established process for the preparation of dimethyl amine.

In our co-pending application No. 209/MAS/2002 there is disclosed and claimed a method for preparation of compound of formula IV which provides a higher yield compared to those described in the prior art.

The inventors have found that in the process of reduction of compound of formula IV the yield could be improved by the use of a very specific solvent system and a most effective form of catalyst combination out of a particular form of Raney Ni catalyst.

In the present system the required amine of formula V is produced at a better yield than that described in the prior art and at the same time there is provided a system which can be handled in a safer way as the system involves no hazardous chemicals and the reduction at pressure of 120 psi of hydrogen is a safer process at which the inventor carried out successful hydrogenation.

In the present invention the methylation of the amine to dimethyl amine has also been optimized.

OBJECTS

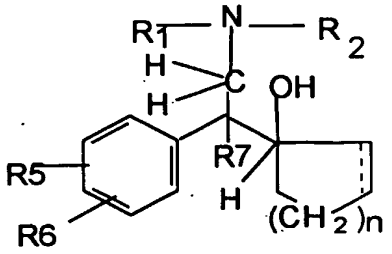
The main objective of the present invention is to produce phenyl ethyl compound of formula II and derivative thereof by an optimised process of reduction through the use of a novel solvent combination which will reduce the cyanocarbinol most effectively.

A further objective of the present invention is to provide a safe method of reduction of the cyano methyl compound of formula IV to amino ethyl carbinol of formula V.

It is yet another objective of the present invention to provide a method for methylating the said amine to the corresponding dimethyl derivative.

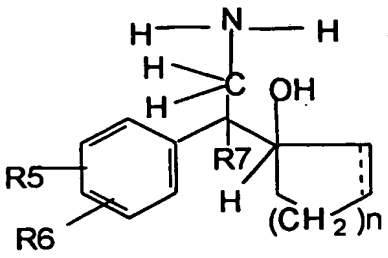
SUMMARY OF INVENTION

A process for the preparation of hydroxy (cycloalkane/cyclokene) phenylethyl amine of the general formula (III)

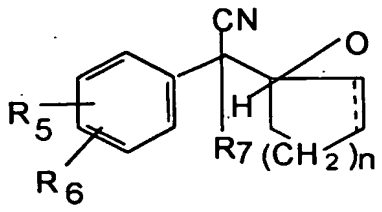


Formula III

comprising alkylation of its precursor amine of general formula (II) which is in turn produced by an effective reduction process from its precursor cyanide having the general formula (I)



Formula II



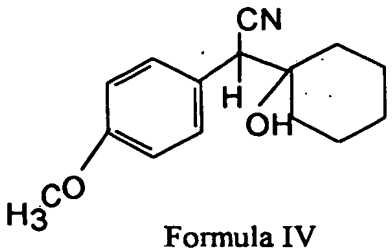
Formula I

where, either of R5 and R6 independently could be in meta or para position and R5, R6 are independently hydrogen, hydroxyl, alkyl, alkoxy, alkanoyloxy, cyano, nitro, alkylmercapto, amino, alkylamino, alkanamido, halo, trifluoromethyl, or taken together methylenedioxy, n is 0,1,2,3,4; R7 is hydrogen or alkyl of 1-7 carbon atom, R1 is H or alkyl of 1-3 carbon atom [illegible] is alkyl of 1-3 carbon atom ,the dotted line represents optional unsaturation.

AILED DESCRIPTION OF THE INVENTION

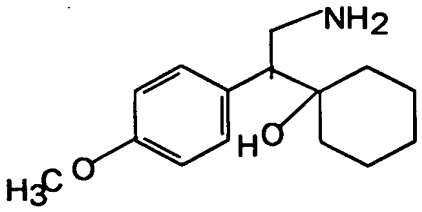
The invention relates to the process for safe manufacture of 1-[2-amino-1-[p-methoxyphenyl)ethyl]cyclohexanol of formula V and methylation of the compound of formula V to the compound 1-[2-dimethyl (p-methoxyphenyl)ethyl]cyclohexanol of formula VI .

In formula I when either R5 or R6 is in para position and either one of them is -OCH3 and the other is H, R7 is hydrogen; the dotted line representing optional unsaturation is removed and n = 2 the compound is a compound of formula IV which is known as 1-[cyano-(p_methoxyphenyl)methyl]cyclohexanol



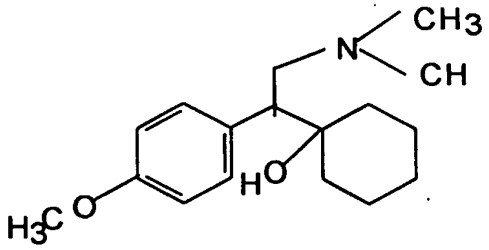
Formula IV

In formula II when either R5 or R6 is in para position and either one of them is –OCH3 and the other is H, R7 is hydrogen; the dotted line representing optional unsaturation is removed and n = 2 the compound is a compound of formula V which is 1-[2-amino-1-(p-methoxyphenyl)ethyl]cyclohexanol obtained by the process of reduction of compound of formula IV



Formula V

n formula I when either R5 or R6 is in para position and one of them is –OCH3 and other one is H; R1 and R2 is –CH3; R7 is H ; n=2 and with optional unsaturation removed it is compounds venlafaxine of formula VI which is obtained by methylation of the compound of formula V



Formula VI

The reduction is carried out using Raney Ni (CORMIII) as catalyst. The reduction is carried out using a solvent media of aqueous ammonia and methanol. Preferably the combination of aqueous ammonia and methanol is in the ratio of between 1:10 to 1:1.Most preferably the ratio of aqueous ammonia to methanol is 1:5.

The catalyst is used in the proportion of 100 to 20 wt. % of the compound of formula IV. Preferably the catalyst concentration is 75% w/w of the compound of formula IV.

The compound of formula IV has a concentration in the range of 2 to 20 w/v % and preferably in the range of 7 to 13 w/v %. Most preferably the concentration is 6 w/v %.

The catalyst is aged upto 120 days after its preparation and prior to its use. Preferably, the catalyst is aged for a period of between 45 to 30 days after its preparation and before its use. Most preferably, the catalyst is aged for 27 days after its preparation and before its use.

The reduction is carried out at temperature of between –5 to 40°C, preferably at 15 to 30°C and most preferably at 27°C.The pressure is in the range of 30 to 200 psi., preferably 50 to 150 psi. and most preferably 120 psi.

The reduction is carried out for 24 hours, preferably between 8 to 24 hours and most preferably upto 9 hours.

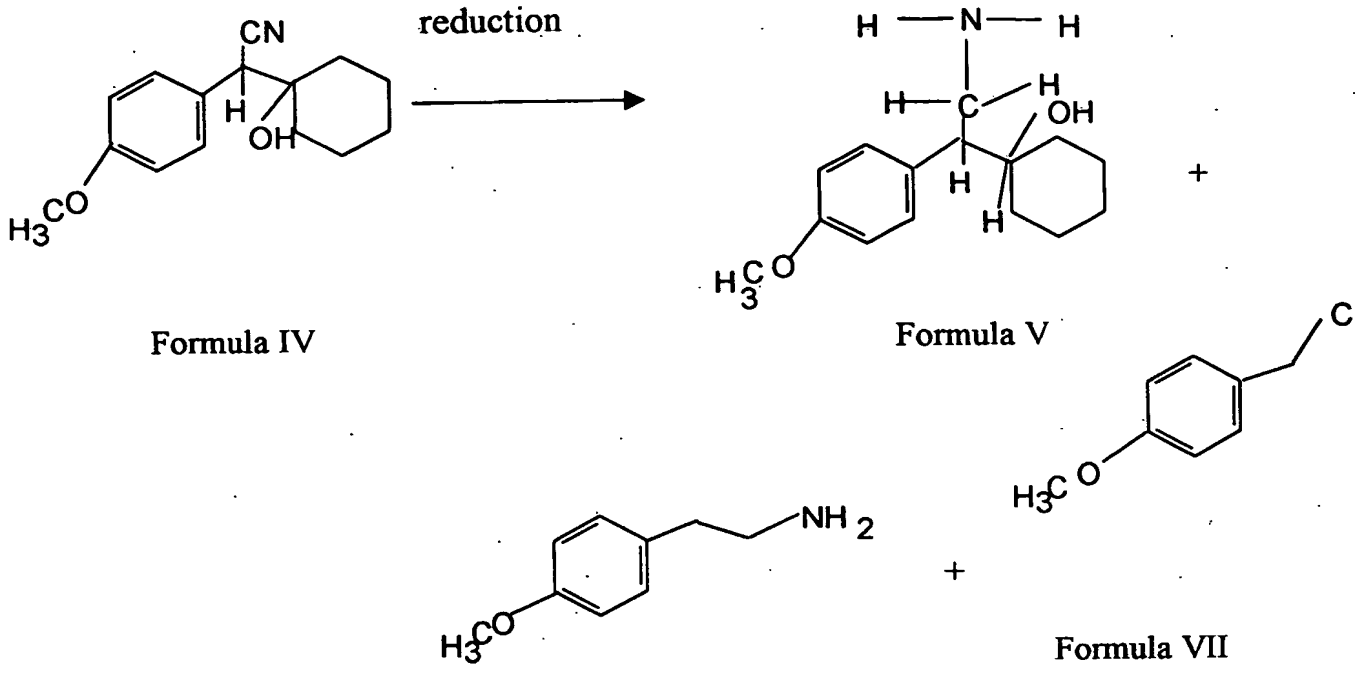
Preferably the methylation is carried using conventional Eschweiler Clarke method.

EXAMPLE

The following process steps are provided to illustrate the invention and are non-limiting examples of the invention

Reduction

Catalytic reduction of compounds of formula IV gives rise to various products which are mixtures of compounds of formula V, VII and VIII. In case of venlafaxine manufacture reduction of compound IV to V various catalyst were tried and results are shown in the table I and II. It is evident from the table as well as following discussion that the reduction process is associated with various by products in different proportion. In this invention effort has been made to increase the yield of the required product V and minimise production of by products .The details discussion illustrates how the reduction as well as methylation step were optimised to get maximum yield and at the same time by products were minimised.



Formula IV

Formula V

Formula VII

Formula VIII

Compound (IV) on subjecting to chemical reduction using catalysts such as LAH, LAH-$AlCl_3$, LAH-H_2SO_4 either lead to compound (VII) by way of its retrogression or there was no reaction at all. Catalytic hydrogenation of compound (IV) using Pd / C at 35 psi and room temperature under neutral as well as acidic conditions gave the starting material back. Similarly, replacing Pd / C by Rh / Al_2O_3 and carrying out the reaction in alcoholic ammonia or acetic acid at 35 psi and room temperature did not give any product. Instead of alcoholic ammonia, when 0.1% NaOH in alcohol was used for the reaction, the reduced retrogression product (VIII) of (IV) was obtained. Finally, hydrogenation of (IV) with 30% w/w of Rh / Al_2O_3 in aq. NH_3-ethanol (1:5) at 35 psi and room temp. could give the required product (V). This compound was used as the reference sample for monitoring hydrogenation reactions using Raney Nickel as the catalyst. Catalytic hydrogenation of compound (IV) over Raney-Ni (50-100% w/w) in alcohol or alcoholic ammonia at 45 to 95 psi and room temperature did not give any product and the starting material was recovered back. Use of 2% alcoholic NaOH or 3-5% of aq. NaOH in alcohol, in place of alcoholic ammonia, resulted in retrogression and subsequent reduction to give compound

(VIII) as the sole product. Finally, with 200% w/w of the Raney Ni catalyst in aq. NH_3-EtOH (1:5) at 35 psi and room temperature, the compound (IV) could be hydrogenated to give the required product (V) in good yield (~90%).

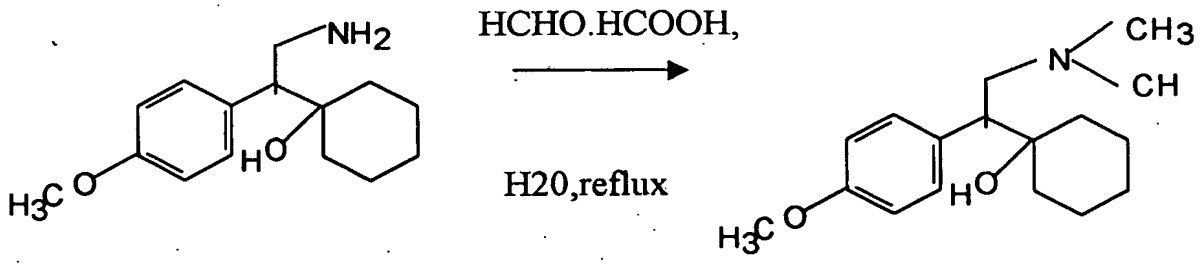
Few more experiments were carried out to see whether lower amounts of the catalyst could be used. In one of such experiment catalyst amount was reduced to 50% w/w, the pressure was increased to 100 psi and the temperature was raised to 50°C. However, it lead to the retrogression followed by reduction and furnished the product(VIII). In another experiment, the catalyst amount taken was 100% w/w, pressure applied was 120 psi and the reaction was carried out at room temp. Interestingly, this reaction gave the required product (V) in good yields. Though, Raney Ni / H_2 system could be used successfully, the reaction always lead to the formation of varying amounts of reduced retrogression product (VIII), without an exception. In order to minimise the formation of compound (VIII) during the reduction of compound (IV), [illegible] parameters were studied in greater detail. The results are summarised below (Table-[illegible]).

The pressure of the reaction was fixed at 120 psi, as that was the upper limit of the pressure available for the scale-up studies in India. Three varieties of Raney Ni catalyst were studied such as Raney Ni-type B, Raney Ni-type F and Raney Ni type CORM-III. A reaction with Raney Ni-type B was very slow and did not go to completion even after 24 hrs. The product formed was the mixture of compound (V) and compound (VII), the former being the major and the latter as minor one. Raney Ni-type F caused complete retrogression and gave the reduced product (VIII). A reaction with Raney Ni CORM-III type could go to completion in 8-9 hrs and formed compound (V) as the major product and compound (VIII) as the minor impurity. Encouraged by such an observation, Raney Ni CORM-III type was selected as the catalyst for further studies. Three different catalyst amounts such as 100% w/w, 75% w/w and 50% w/w were studied and it was found that 50% w/w catalyst required 16 hrs for the completion of the reaction, whereas, 75% w/w and 100% w/w catalysts could bring about the reaction to completion in 8-9 hrs. Therefore, 75% w/w amount of the catalyst was taken for further studies. The substrate concentration was studied from 1.6% w/v to 12% w/v and it was found that upto 6% w/v substrate concentration the retrogression is minimum and thereafter the

amount of the retrogression product goes on increasing. The reaction goes smooth at 27°C, the rise in temperature leads to retrogression and at 50°C the reaction gives only the retrogression product (VIII). Raney Nickel catalyst is usually accompanied with a base (NaOH). The traces of base present during hydrogenation, at high pressure, leads to the retrogression. Therefore, the catalyst needs to be washed thoroughly with water before use. Washing the catalyst with 5% acetic acid followed by water did not significantly reduced the concentration of the retrogression product (VIII).

Therefore, washing of the catalyst with excess water was considered to be sufficient to remove the traces of alkali present with the catalyst. The age of the catalyst was also found to play some role in the formation of retrogression product (VIII). The catalyst of the age of three weeks and above gave minimum amount of the retrogression product. Finally, in the optimised conditions, 75% w/w Raney Ni CORM-III catalyst with 3 weeks aging was used after repeated washings with water at 6% w/w substrate conc. In aqueous ammonia-methanol solvent maintained at 27°C under 120 psi Hydrogen pressure for 8-9 hrs. The yield of the product under these conditions was about 90% and contained about 89% of the required product (V) and 5% of the retrogression product (VIII). The impurity, VIII , was removed in the subsequent step.

Step-3 : Methylation



Formula V Formula VI

After the successful reduction of the nitrile function to the amino group, the next task was to carry out the methylation of the amino function. As per the literature, such a conversion can be carried out using Eshwieler Clarke conditions. In the present case we also carried on the same

Eshwieler Clarke reaction for converting compound (V) to compound (VI). In a typical experiment compound (V) was refluxed with formaldehyde, formic acid and water for about 16 hrs. After the work-up the methylated product was directly treated with

IPA.HCl The hydrochloride salt of Venlafaxine was precipitated out whereas, the hydrochloride salt of the reduced retrogression product (VIII) remained in the solution. The final product was well characterized from its spectral data, m.p. and HPLC.

Certain modifications were tried in this step in view of optimizing the yields. In one of the modifications, sodium formate was added to the Eshwieler Clarke reaction mixture. It is supposed to minimize the formylation of amine and thereby increase the yield of the required product. However, in the present case it did not significantly increase the yield of the reaction. In another modification the sequence of addition of formaldehyde and formic acid was reversed. However, this lead to the decrease in yield. In yet another modification, the reaction time was varied from 16 to 18 hrs or 30 hrs. However, in [illegible] was no increase in the product yield.

Mass Spectra Analysis :

Molecular weight : 249 [$(M+1)^+$ by C.I.M.S.]

Table I : Results of Condensation Reaction for cyano carbinol

Sr. No.	Expt. No.	Mol ratio (2/1)	Base (equiv.)	Catalyst (equiv.)	Solvent	Temp. (^{0}C)	Time (hrs.)	Yield (%)
1	VDG / 00 / 01	1.05	n-BuLi	-	THF	-78	3	82
2	VDG / 00 / 02	1.10	n-BuLi	-	THF	-30	3	72
3	VDG / 00 / 03	1.10	n-BuLi	-	THF	-5	-	-
4	VDG / 00 / 04	1.00	$NaNH_2$	-	THF	-78	3	62
5	VDG / 00 / 05	1.00	$NaNH_2$	-	THF	-5	2	30
6	VDG / 00 / 06	1.00	50% NaOH	TBB	H_2O	27	3	Very Poor
7	VDG / 00 / 07	1.00	50% NaOH	Cetrimide	H_2O	27	3	Very Poor
8	VDG / 00 / 08	1.00	50% NaOH	TBAB	H_2O	27	3	Very Poor
9	VDG / 00 / 09	1.10	10% NaOH (0.46 eq.)	TBAB (0.002 eq.)	H_2O	27	3-4	82
10	VDG / 00 / 10	1.10	10% NaOH (0.46 eq.)	TBAB (0.002 eq.)	H_2O	27	8	82
11	VDG / 00 / 11	1.30	10% NaOH (0.46 eq.)	TBAB (0.002 eq.)	H_2O	27	8	90
12	VDG / 00 / 12	1.35	10% NaOH (0.46 eq.)	TBAB (0.002 eq.)	H_2O	27	8	90
13	VDG / 00 / 13	1.50	10% NaOH (0.46 eq.)	TBAB (0.002 eq.)	H_2O	27	8	83
14	VDG / 00 / 14	1.40	10% NaOH (1.0 eq.)	TBAB (0.002 eq.)	H_2O	27	3	92
15	VDG / 00 / 15	1.10	10% NaOH (0.46 eq.)	TBAB (0.001 eq.)	H_2O	27	3	92
16	VDG / 00 / 16	1.40	10% NaOH (0.46 eq.)	TBAB (0.002 eq.)	H_2O	18	6	91
17	VDG / 00 / 17	1.35	10% NaOH (0.46 eq.)	TBAB (0.002 eq.)	H_2O	18	6	91
18	VDG / 00 / 18	1.35	10% NaOH (1.0 eq.)	TBAB (0.002 eq.)	H_2O	15	3	92

Table II : Reduction of C[illegible] (IV) using different catalysts

Sr. No.	Expt. No.	Catalyst (% w/w)	Solvent	Concn. (% w/v)	P (psi)	Temp. (^{0}C)	Time (hrs.)	Product
1	VDG / 00 / 19	LAH	THF	-	-	RT	15	1
2	VDG / 00 / 20	LAH - $AlCl_3$	Ether	-	-	RT	15	1
3	VDG / 00 / 21	LAH - H_2SO_4	THF	-	-	0	4	Nil
4	VDG / 00 / 22	H_2 / 5% Pd-C (20)	MeOH	-	-	RT	15	Nil
5	VDG / 00 / 23	H_2 / 5% Pd-C (20)	Dioxane	-	35	RT	4	Nil
6	VDG / 00 / 24	H_2 / 10% Pd-C (20)	IPA - AcOH	-	35	RT	4	Nil
7	VDG / 00 / 25	H_2 / 10% Pd-C (20)	IPA . HCl	-	35	RT	4	Nil
8	VDG / 00 / 26	H_2 / 10% Pd-C (35)	AcOH	-	35	RT	4	Nil
9	VDG / 00 / 27	H_2 / Rh - Al_2O_3 (20)	Methanolic NH_3	-	35	RT	4	Nil
10	VDG / 00 / 28	H_2 / Rh - Al_2O_3 (43)	Ethanolic NH_3	-	35	RT	3	Nil
11	VDG / 00 / 29	H_2 / Rh - Al_2O_3 (25)	0.1% NaOH - EtOH	-	35	RT	3	8
12	VDG / 00 / 30	H_2 / Rh - Al_2O_3 (20)	10% NaOH - EtOH	-	35	RT	3	8
13	VDG / 00 / 31	H_2 / Rh - Al_2O_3 (20)	AcOH	-	35	RT	3	Nil
14	VDG / 00 / 32	H_2 / Rh - Al_2O_3 (30)	Aq. NH_3 - MeOH (1 : 5)	-	35	RT	9	4
15	VDG / 00 / 33	H_2 / Rh - Al_2O_3 (100)	Aq. NH_3 - MeOH (1 : 5)	-	35	RT	9	4
16	VDG / 00 / 34	H_2 / Rh - Al_2O_3 (70)	Aq. NH_3 - MeOH (1 : 5)	-	35	RT	9	4

Table II : Reduction of Compd. (IV) using different catalysts

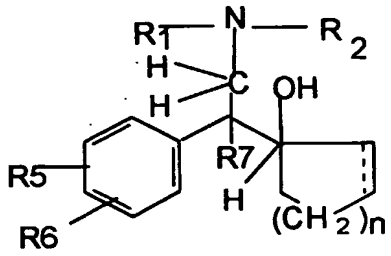
Sr. No.	Expt. No.	Catalyst (% w/w)	Solvent	Concn. (% w/v)	P (psi)	Temp. (^{0}C)	Time (hrs.)	Product
17	VDG / 00 / 35	H_2 / Raney Ni (10)	Methanolic NH_3	-	45	RT	2	Nil
18	VDG / 00 / 36	H_2 / Raney Ni (10)	Methanolic NH_3	-	95	RT	3	Nil
19	VDG / 00 / 37	H_2 / Raney Ni (30)	Methanolic NH_3	-	45	RT	4	Nil
20	VDG / 00 / 38	H_2 / Raney Ni (30)	Methanolic NH_3	-	45	RT	10	Nil
21	VDG / 00 / 39	H_2 / Raney Ni (100)	5% NaOH - MeOH	-	35	RT	1.5	8
22	VDG / 00 / 40	H_2 / Raney Ni (50)	5% NaOH - MeOH	-	35	RT	2.5	8
23	VDG / 00 / 41	H_2 / Raney Ni (50)	3% NaOH - MeOH	-	35	RT	2.5	8
24	VDG / 00 / 42	H_2 / Raney Ni (100)	MeOH	-	35	RT	2.5	Nil
25	VDG / 00 / 43	H_2 / Raney Ni (50)	2% Ethanolic NaOH	-	35	RT	2.5	8
26	VDG / 00 / 44	H_2 / Raney Ni (25)	2% Ethanolic NaOH	-	35	RT	2.5	8
27	VDG / 00 / 45	H_2 / Raney Ni (50)	Ethanolic NH_3	-	120	50	10	8
28	VDG / 00 / 46	H_2 / Raney Ni (50)	Aq. NH_3 - EtOH (1 : 5)	-	100	50	8	8
29	VDG / 00 / 47	H_2 / Raney Ni (200)	Aq. NH_3 - EtOH (1 : 5)	2.0	35	RT	18	4
30	VDG / 00 / 48	H_2 / Raney Ni (100)	Aq. NH_3 - EtOH (1 : 5)	1.6	120	RT	8	4
31	VDG / 00 / 49	H_2 / Raney Ni (50)	Aq. NH_3 - EtOH (1 : 5)	6.0	225	RT	8	4
32	VDG / 00 / 50	H_2 / Raney Ni (25)	Aq. NH_3 - EtOH (1 : 5)	6.0	225	RT	13	4

Table III : Reduction of compound (IV) using Raney Ni (CORM III) in aq. NH_3-alcohol (1:5) at 120 psi

Sr. No.	Expt. No.	Batch size (g.)	Solvent	Conc. (% w/v)	Cat. Amt. (% w/w)	Cat. Age (days)	Temp. (^{0}C)	Time (hrs.)	Crude pdt. (% Yield)	Product V (%)	Impurity VIII (%)
1	VDG / 00 / 51	5	Aq.NH_3-EtOH (1:4)	1.6	100	5	27	8	94	84	16
2	VDG / 00 / 52	21	Aq.NH_3-EtOH (1:4)	7	47.6	33	27	15	74	78	22
3	VDG / 00 / 53	1800	Aq.NH_3-EtOH (1:4)	12	75	39	27	12	-	28	72
4	VDG / 00 / 54	72	Aq.NH_3-MeOH (1:4)	12	75	69	27	10	88	85	15
5	VDG / 00 / 55	72	Aq.NH_3-MeOH (1:4)	12	75	70	27	12	88	86	14
6	VDG / 00 / 56	180	Aq.NH_3-MeOH (1:4)	6	75	110	25	12	84	82	18
7	VDG / 00 / 57	72	Aq.NH_3-MeOH (1:4)	12	75	21	27	11	90	38	62
8	VDG / 00 / 58	180	Aq.NH_3-MeOH (1:4)	6	75	[illegible]	27	10	89	89	11
9	VDG / 00 / 59	72	Aq.NH_3-MeOH (1:4)	6	75	[illegible]	27	12	91	82	18
10	VDG / 00 / 60	36	Aq.NH_3-MeOH (1:4)	6	75	[illegible]	30	10	75	75	25
11	VDG / 00 / 61	36	Aq.NH_3-MeOH (1:4)	6	75	[illegible]	30	10	85	80	20
12	VDG / 00 / 62	36	Aq.NH_3-MeOH (1:4)	6	75	75	24	12	-	87	13

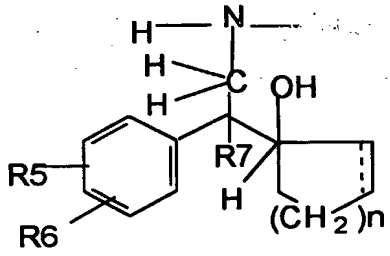
CLAIM :

1. A process for the preparation of hydroxy (cycloalkane/cyclokene) phenylethyl amine of the general formula (III)

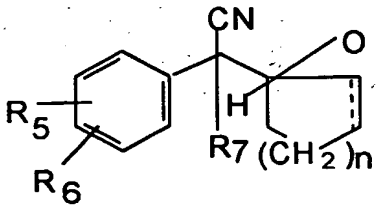


Formula III

comprising alkylation of its precursor amine of general formula (II) which is in turn produced by an effective reduction process from its precursor cyanide having the general formula (I)



Formula II

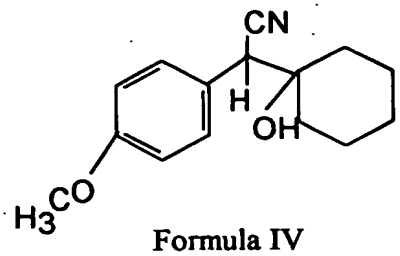


Formula I

where, either of R5 and R6 independently could be in meta or para position and R5, R6 are independently hydrogen, hydroxyl, alkyl, alkoxy, alkanoyloxy, cyano, nitro, alkylmercapto, amino, alkylamino, alkanamido, halo, trifluoromethyl, or taken together methylenedioxy, n is 0,1,2,3,4; R7 is hydrogen or alkyl of 1-7 carbon atom,.R1 is H or alkyl of 1-3 carbon atom and R2 is alkyl of 1-3 carbon atom ,the dotted line represents optional unsaturation.

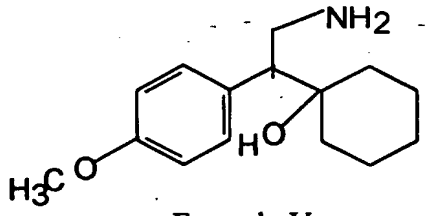
2. A process as claimed in claim 1 wherein, in formula I, when either R5 or R6 is in para position and either one of them is -OCH3 and the other is H, R7 is hydrogen; the dotted line

representing optional unsaturation is removed and n = 2 the compound is a compound of formula IV which is known as 1-[cyano-(p_methoxyphenyl)methyl]cyclohexanol.



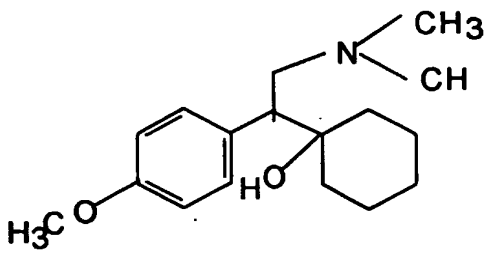
Formula IV

3. A process as claimed in claim 1 wherein, in formula II, when either R5 or R6 is in para position and either one of them is –OCH3 and the other is H, R7 is hydrogen; the dotted line representing optional unsaturation is removed and n = 2 the compound is a compound of formula V which is 1-[2-amino-1-(p-methoxyphenyl)ethyl]cyclohexanol obtained by the process of reduction of compound of formula IV



Formula V

4. A process according to claim 1 wherein, in formula I, when either R5 or R6 is in para position and one of them is –OCH3 and other one is H; R1 and R2 is –CH3; R7 is H ; n=2 and with optional unsaturation removed ,the compound is venlafaxine of formula VI which is obtained by methylation of the compound of formula VI



Formula VI

5. A process as claimed in claim 1 or 3, wherein the reduction is carried out using Raney Ni (CORMIII) as catalyst.

6. A process as claimed in claim 5, wherein the reduction is carried out using a solvent media of aqueous ammonia and methanol.

7. A process as claimed in claim 5, wherein the reduction is carried out in the presence of the combination of aqueous ammonia and methanol in the ratio of between 1:10 to 1:1.

8. A process as claimed in claim 7, wherein the ratio of aqueous ammonia to methanol is 1:5.

9. A process as claimed in claim 5, wherein the catalyst is used in the proportion of 100 to 20 wt. % of the compound of formula IV.

10. A process as claimed in claim 9, where the catalyst has been used most effectively at a concentration of 75% w/w of the compound of formula IV.

11. A process as claimed in claims 1 or 2, wherein the compound of formula IV has a concentration in the range of 2 to 20 w/v %.

12. A process as claimed in claim 12, wherein compound of formula IV has a concentration in the range of 7 to 13 w/v %.

13. A process as claimed in claim 12, wherein the compound of formula IV has a concentration of 6 w/v %.

14. A process as claimed in any one of the preceding claims wherein the catalyst is aged upto 120 days after its preparation and prior to its use.

15. A process as claimed in claim 14 wherein the catalyst is aged for a period of between 45 to 30 days after its preparation and before its use.

16. A process as claimed in claim 15, where the catalyst is aged for about 27 days after its preparation and before its use.

17. A process as claimed in any one of the preceding claims, wherein the reduction is carried out at –5 to 40°C.

18. A process as claimed in claim 17, wherein the reduction is carried out at 15 to 30°C.

19. A process as claimed in claim 18, wherein the reduction is carried out at 27°C.

20. A process as claimed in any one of claims 17 to 19, wherein the reduction is carried out for 24 hours.

21. A process as claimed in claim 20, wherein the reduction is carried out for a period of between 8 to 24 hours.

22. A process as claimed in claim 21 wherein the reduction is carried out upto 9 hours.

23. A process a claimed in claim 1 and 3 wherein the hydrogen pressure is maintained between 30 to 200 psi.

24. A process a claimed in claim 23, wherein the hydrogen pressure is maintained from 50 to 150 psi.

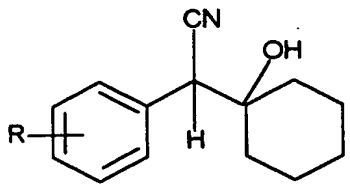
25. A process a claimed in claim 24, wherein the hydrogen pressure is maintained at 120 psi.

26. A process as claimed in any one of the preceding claims, wherein the methylation is carried out using conventional Eshweiler Clarke method.

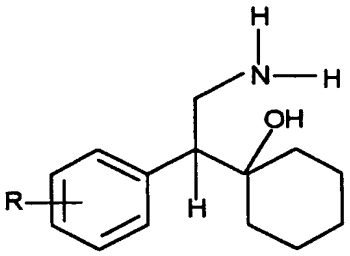
AMENDED CLAIMS

[received by the International Bureau on 02 April 2003 (02.04.03);
original claim 1 amended; new claims 2-5;
original claims 2, 6, 15, 17, 19, 20, 21 renumbered;
claims 3, 4, 5, 7-16, 23, 24, 26 deleted (2 pages)]

1. Process for preparation of hydroxy (cycloalkane) phenyl ethyl amine by reduction of cyano compound of formula 1 using Raney Nickel CORM III having bulk density between 0.40 to 0.60 gm/cc as catalyst



Formula I



Formula II

where, R is in meta or para position and is independently hydrogen, hydroxyl, alkyl, alkoxy, alkanoyloxy, amino, alkyl amino, alkanamido, halo and triflouro methyl.

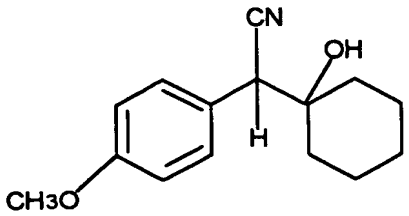
2. Process according to claim 1, wherein the said Raney Nickel has a particle size of 40 to 50 μm.

3. Process according to any of claim 1 or 2, wherein said Raney Nickel comprises 86 to 88 wt% Nickel and 8 to 10 wt% Aluminum.

4. Process according to any of claims 1 to 3, wherein said Raney Nickel has nitrobenzene activity between 55 – 65 ml. /gm. / min of Hydrogen.

5. Process according to any of claims 1 to 4, wherein said Raney Nickel has susceptibility to dehalogenation less than 1%.

6. Process according to claim 1, wherein R is in para position and is $-OCH_3$ and the compound of formula 1 is 1-[cyano-(p-methoxyphenyl)methyl]cyclohexanol, a compound of formula III.



Formula III

7. Process according to claim 1, wherein said reduction is carried out in solvent of aqueous ammonia and methanol.

8. Process according to claim 1, wherein said reduction is carried out at temperature between -5 to 40^{0}C.

9. Process according to claim 8, wherein said temperature is between 15 to 30^{0}C.

10. Process according to claim 9, wherein said temperature is 27^{0}C.

11. Process according to any of the preceding claims, wherein said reduction is carried out for a period of 24 hours.

12. Process according to claim 11, wherein said reduction is carried out for a period of 8 to 24^{0}C.

13. Process according to claim 12, wherein said reduction is carried out for a period of 9 hours.

14. Process according to any of the preceding claims, wherein said reduction is carried out at a pressure of 120 psi of hydrogen.

STATEMENT UNDER ARTICLE 19 (1)

Re: PCT International Application No. PCT/IN02/00131 dated 13th June 2002
Applicant: Global Bulk Drugs & Fine Chemicals Pvt. Ltd.
Title: MANUFACTURE OF PHENYL ETHYL AMINE COMPOUNDS
Priority Date: 26/03/2002.
Agent's File Ref. : FPAA/167 (PCT).

STATEMENT UNDER ARTICLE 19

The subject patent application relates to a process for preparation of hydroxy (cycloalkane) phenyl ethyl amine by reduction of cyano compound, as represented by Formula 1 in the specification, using Raney Nickel CORM III as catalyst. The use of Raney Nickel CORM III as catalyst results in surprisingly higher yields of the product. The yield by the process of the invention is about 90%, being substantially higher than yields reported in the known processes which are in the range of 15 to 30%. Using this catalyst, the process also requires lower reaction temperatures, reaction time and hydrogen pressure thus making the reaction parameters more suitable for industrial application while maintaining the high yield.

With regard to the prior art cited in the International Search Report, the applicants state that process for preparation of hydroxy (cycloalkane) phenyl ethyl amine by reduction of cyano compound is known in the art. Thus, in view of the prior art and in order to distinguish the claimed invention more clearly from the prior art, the applicants have now incorporated reference to the specific catalyst namely Raney Nickel CORM III in claim 1.

Regarding the catalyst, the applicants wish to clarify that CORM III (also known as KALCAT 1961) is a commercially available form of Raney Nickel which is distinct from the known variety of Raney Nickel catalyst in terms of bulk density, particle size, composition, nitrobenzene activity and susceptibility to dehalogenation. Thus, in order to characterize this specific form of the Raney Nickel in the claims, the applicants have now incorporated the characteristics of CORM III namely the bulk density in claim 1. The bulk density is a critical parameter of the catalyst with respect to porosity and pore size. Due to its higher porosity and bigger pore size Raney Nickel CORM III has better activity compared to conventional Raney Nickel. Additionally, the catalyst particle size and composition of the catalyst are preferred features which have also now been brought out in sub claims.

The applicants have now restricted the process to the preparation of hydroxy (cycloalkane) phenyl ethyl amine by reduction of cyano compound, thus narrowing the scope of the product (Formula 1) prepared by the process. The claims have also been further amended to avoid possible overlaps with prior art and to more clearly bring out the inventive features.

The particle size, bulk density, nitrobenzene activity and dehalogenation susceptibility of CORM III have been brought out in amended claims 2, 3, 4 and 5.

Regarding the rest of the claims, only claims 2, 6, 17, 18, 19, 20, 21, 22 and 25 of the originally filed set of claims have been maintained with necessary consequential amendments in view of amended claim 1.

Original claims 6, 17, 18, 19, 20, 21, 22 and 25 are renumbered as 5, 6, 7, 8, 9, 10, 11 and 12 respectively with corresponding amendments in the appendencies.

Corresponding amendments in the text will be effected at a later stage.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IN 02/00131

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C213/02 C07C215/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, INSPEC, COMPENDEX, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 350 912 B1 (KAMAT SUBHASH KRISHNAJI ET AL) 26 February 2002 (2002-02-26) the whole document	1-5, 9-18, 21-26
Y	US 2 462 736 A (GRESHAM WILLIAM E) 22 February 1949 (1949-02-22) the whole document	1-26
X	US 4 535 186 A (HUSBANDS G E [illegible] AL) 13 August 1985 (1985-08-13) cited in the application	1-4,14, 15,23,26
Y	column 2, line 49 -column 3, line 60; claims 1-4; examples 1-3	1-26

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 November 2002	20/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seelmann, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

nal Application No
PCT/IN 02/00131

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	FRISTAD W E ET AL: "MANGANESE(III) GAMMA-LACTONE ANNULATION WITH SUBSTITUTED ACIDS" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 50, no. 17, 1985, pages 3143-3148, XP000996322 ISSN: 0022-3263 page 3178, left-hand column, line 27 - line 41	1-26

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IN 02/00131

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 6350912	B1	26-02-2002	NONE	
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